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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,045	POTTER, DAVID A.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *6-11,15,18-26 and 30-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,12-14,16,17,27-29 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/4/04 & 5/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-60 are presented for examination.

Acknowledgement is made of Applicant's clam for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/399,573, filed July 26, 2002. Applicant's Information Disclosure Statements (IDS) filed March 4, 2004 (two pages) and May 10, 2004 (one page) have each been received and entered into the application. As reflected by the attached, completed copies of form PTO-1449 (three pages total), the Examiner has considered the cited references.

Applicant's response filed October 31, 2005 to the requirement for restriction/election dated September 28, 2005 has also been received and entered into the application.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group I (claims 2-5, 14-26 and 57-60), drawn to a method for treating an HIV-negative patient who has cancer, comprising administering to the patient a therapeutically effective amount of a compound of formula I or formula I in combination with formula II, and the election of species (iii), drawn to an anticancer agent other than ritonavir, lopinavir or amprenavir, and further election of the species of anticancer agent (g), drawn to the antimicrotubule agents paclitaxel or docetaxel, in the reply filed October 31, 2005 has been acknowledged by the Examiner.

For the purposes of examination, claims 1-5, 12-13, 16-17, 27-29 and 60 have been identified as reading on both the elected method and the elected species of antimicrotuble agents (i.e., paclitaxel or docetaxel).

Therefore, for the reasons above and those made of record at pages 2-9 of the previous Office Action dated September 28, 2005, the restriction requirement is deemed proper and is made **FINAL**.

Claims 6-11, 15, 18-26 and 30-59 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are 1-5, 12-14, 16-17, 27-29 and 60 and such claims are herein acted on the merits.

Applicant's Claim for Priority Under 35 U.S.C. §119(e)

The complete disclosure of U.S. Provisional Patent Application No. 60/399,573, filed July 26, 2002, to which the present application claims benefit under 35 U.S.C. §119(e) has been considered. Sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter has been noted. Accordingly, for the purposes of examination and the application of prior art, the effective filing date of the present application is considered to be the filing date of U.S. Provisional Patent Application No. 60/399,573 (July 26, 2002).

Objections to the Specification

The use of the trademarks NORVIR, KALETRA, AGENERASE (see page 1, line 25 and page 15, line 13), CRIXIVAN (see page 15, line 13), VIRACEPT (see page 15, line 15), INVIRASE (see page 15, line 16), FORTOVASE (see page 15, line 16) and IRESSA and TARCEVA (see page 5, line 24 and page 11, line 21) has been noted in this application. Each

letter of the trademark should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

The disclosure is further objected to because it contains an embedded hyperlink and/or other form of browser-executable code as found at lines 9-10 of page 9 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. Please reference MPEP § 608.01.

The specification is objected to for failing to provide sequence ID numbers for the peptide sequences provided at page 21 of the disclosure. See, particularly, lines 17-18, 25 and the line bridging pages 21 and 22.

Appropriate correction is required.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 12-14, 16-17, 28-29 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pancreatic, lung, breast, head and neck, prostate, colon, stomach, ovarian or brain cancer, fails to reasonably provide enablement for the treatment or prevention of human cancer, in general, as recited in or

encompassed by, for example, claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

It is noted that while Applicant has not expressly claimed the "prevention" of human cancer in general in the present claims, the disclosure of the present application teaches the use of the presently claimed agents for prophylaxis and chemoprevention, prior to a definitive diagnosis of cancer (see page 13, line 11-page 15, line 5). Thus, because the claims are read in light of the specification, the present claims read on the prophylaxis or prevention of cancer in general. For these reasons, the present rejection is properly set forth insofar as the present claims read upon the treatment or prevention or prophylaxis of cancer in general.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1 and 2) The claimed invention is directed to a method for treating an HIV-negative patient who has cancer, comprising the administration of a therapeutically effective amount of a composition comprising the compound defined by Formula I and, optionally, in combination with the compound defined by Formula II, and/or other anticancer agents, such as the antimicrotubule agents paclitaxel or docetaxel (see present claim 1, for example).

3 and 7) In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that all types of human cancer could be effectively treated or prevented by the administration of the claimed active agent(s). Based on the state of the art, as discussed below, the artisan would have only accepted that the incidence of such a condition could be reduced, rather than that it could actually be prevented from ever occurring.

As set forth in *In re Marzocchi et al.,* 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

In particular, the term "prevent" in the present claims is considered to circumscribe a method of absolute success. That is, in order to be enabled to practice the present invention, the

skilled artisan would have to accept that by administering the presently claimed active agent(s), the incidence of human cancer would be 0% and there would be reasonable guarantee that such a condition would never develop. Such a situation is sufficiently unusual that data would need to be shown in order to establish that any type of human cancer could be kept from ever occurring through the administration of the claimed active agents. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as highly complex as cancer, the specification, which lacks an objective showing that such a condition could be prevented, is viewed as lacking an enabling disclosure of the same.

Similarly, the skilled artisan would also have to accept that by administering the presently claimed active agent(s), all known types of human cancer may be treated. Such a situation is also sufficiently unusual that data would need to be shown in order to establish that any type of human cancer could be effectively treated through the administration of the presently claimed active agent(s). As stated previously, because absolute success is not reasonably possible with most diseases or disorders, especially a condition as highly complex as cancer, the specification, which lacks an objective showing that all known types of human cancer could be treated, is, again, viewed as lacking an enabling disclosure of the same.

Here, the objective truth of the statement in claim 1 that human cancer of any type may be treated or prevented is doubted because, while the state of the art of cancer treatment is well developed with regard to the *treatment* of *specific* cancer types (see Cecil's Textbook of Medicine at page 1060-1074), the state of the art with regard to *treating or preventing* cancer *in general* is grossly underdeveloped.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no

known anticancer agent or combination of anticancer agents that is effective against treating all cancer or neoplasm types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer or neoplastic cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer or neoplastic cells for each and every type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Furthermore, there is no therapeutic modality known in the art that is capable of preventing cancer or neoplasm in general. Cecil's states, "Although current systemic therapy can cure few forms of metastatic cancer, it is now increasingly effective as a component of multimodal management of apparently localized cancers known to have a high frequency of occult micrometastatic spread" (see page 1060, column 1, paragraph 2). The pathophysiological manifestations of cancer are elusive and are generally capable of evading detection until extensive metastatic spread has already occurred. While surgical resection gives the best option for cure, such is not recognized to guarantee the prevention of metastases, since microscopic drift of cancerous cells may occur in the body and cause peripheral metastases far from the primary site. In addition, the art does not recognize a method of cancer prevention, particularly because the development of cancer may be attributed to a variety of factors, such as lifestyle (e.g., smoking, obesity, lack of exercise), genetics, or other ubiquitous factors, such as environmental hazards and stress. The art has not currently identified a way of eliminating such predisposing factors and, thus, preventing the development of cancer. As a result, the predictability of

preventing cancer using any of the therapeutic modalities known in the art is highly variable and cannot be guaranteed.

Given that there was not known any specific agent or combination of agents effective to treat or prevent all known types of cancer, one of ordinary skill in the art would not accept on its face Applicant's statement that all known types of cancer could be treated or prevented. The artisan would have required sufficient direction as to which specific types of cancer could be treated with the presently claimed active agents and, further, how the artisan could predict the patient population in need of prevention of specific cancer types (i.e., how the population in need of prevention would have been determined), such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that absolute prevention is an outcome not reasonably expected by one of ordinary skill in the art and to the artisan, the concept of a single agent, or even a combination of agents, that is effective to treat or prevent all known types of cancer would have been unique and, thus, met with a great deal of skepticism.

4) Applicant has merely disclosed that by administering the claimed active agent(s), one may treat or prevent any type of human cancer. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed agent(s), can be employed to accomplish the prevention of such a condition in a predictable manner.

5) The specification at pages 23-35 provides data demonstrating that the use of a composition comprising ritonavir is capable of reducing the proliferation of breast, colon or lung cancer cells. Such data, however, is not commensurate in scope with the claimed subject matter.

While the present claims encompass *treating or preventing all known types* of cancer by administering the claimed active compound(s), Applicant's data merely establishes that the administration of these compounds can merely *treat or reduce* the risk of pancreatic, lung, breast, head and neck, prostate, colon, stomach, ovarian or brain cancer. However, no data has been provided that shows the claimed composition is capable of definitively treating or preventing the development of any known type of cancer.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of human cancer, there is no apparent data to support the contention that the use of the claim specified active agent(s) could actually treat or prevent any known type of cancer by simply administering, by any method, an amount of the claimed active agent(s), since the present specification fails to enable one of ordinary skill in the art to practice the presently claimed invention.

6) The burden of enabling the treatment or prevention of all types of human cancer is much greater than that of enabling the treatment of the specific types of cancer shown to be responsive to such treatment. Since the present specification would not enable the skilled artisan to prevent such a condition, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the present invention.

8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the treatment or prevention of human cancer of any type could be achieved. In order to actually achieve the treatment or prevention of this condition in general, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant has failed to demonstrate, that all types of human cancer could actually be treated or prevented, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-5, 12-13, 16-17, 28-29 and 60 are deemed properly rejected.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I Claims 1-5, 12-13, 16-17, 27-29 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "prodrug" in claim 1, for example, is a relative term that renders the claims indefinite. In particular, "prodrug" does not particularly point out the degree or type of derivation that a given compound may have in relation to the parent compound and still be considered a "prodrug" as intended by Applicant. Applicant has failed to provide any specific

definition for this term in the present specification. Lacking a clear meaning of the term "prodrug", the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seeks patent protection.

In the present specification at page 16, lines 14-17, Applicant has set forth:

> "A 'pharmaceutically acceptable prodrug' means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention, which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound useful in the methods of this invention."

Such disclosure, however, does not render the claims definite. Words and phrases in the claims must be given their "plain meaning" as understood by one having ordinary skill in the art unless defined by Applicant in the specification with "reasonable clarity, deliberateness and precision" (MPEP §2111.01). Here, Applicants' definition of "prodrugs" is not reasonably clear, deliberate or precise because the definition does not specify what compounds may be considered prodrugs. That is, the definition is presented in a non-limiting manner. Thus, the identity of those compounds that are included or excluded by the term "prodrug" is open to subjective interpretation.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112, second paragraph and, thus, are properly rejected.

II Claims 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The expression "a cancer associated with resistance to known anticancer drug regimens" is a phrase that renders the claims indefinite. It is not clear as to whether Applicant is intending

to claim the treatment of any type of cancer that has shown resistance to any known anticancer agent or whether Applicant is intending to claim any type of cancer resulting from drug resistance that has that emerged from previous treatment with known anticancer agents.

The recitation of the word "associated" does not define the metes and bounds of the claim because Applicant has failed to convey the relationship between the cancer and the resistance to other known anticancer drugs that has been demonstrated. Furthermore, claim 29 fails to cure such a defect in the claims. While it is noted that the cancer must contain cells that express P-glycoprotein, multidrug-resistance associated protein or breast cancer resistance protein, it remains that the claims fail to properly delimit the cancers that are intended to be within the scope of the claim and how they are related or "associated" with drug resistance.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112, second paragraph and, thus, are properly rejected.

For the purposes of examination, claims 28-29 will be interpreted to read upon the specific types of cancers that are recited in present claim 27.

III Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The MPEP sets forth the following at §2173:

> "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification

> meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (See MPEP §2173).

The term "approximately" in the expression "wherein the amount, by weight, of the compound of Formula II or a pharmaceutically acceptable salt or prodrug thereof is approximately four times greater than the amount, by weight of the compound of Formula I" (see present claim 5, for example) is a relative term that renders the claim indefinite. The expression "approximately" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use of such a term would invite subjective interpretations of whether or not a particular amount by weight is included in or excluded from the present claims and what degree of variability outside the recited ranges is within the scope of the claims. In light of such, the public would not be reasonably informed of the boundaries of what constitutes infringement of the present claims.

For these reasons, the claims do not meet the tenor and express requirements of 35 U.S.C. §112, second paragraph and are, therefore, properly rejected.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 12, 14 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Weichold et al. (WO 00/33654; 2000) in light of The Merck Index (cited to show a fact).

In accordance with the MPEP at §2131.01, it is proper to rely on a second reference for a rejection under 35 U.S.C. 102 in order to show the meaning of a term used in the primary reference.

Weichold et al. teach a method of treating pancreatic (page 33, line 25), lung (page 33, line 25), breast (page 33, line 25), head and neck (page 33, line 26), prostate (page 33, line 25), colon (page 33, line 26), stomach (page 33, line 25), ovarian (page 33, line 26) and brain cancer (page 33, line 26; see present claims 1 and 27 for each of the previously named cancer types) using at least one HIV-1 protease inhibitor (page 33, lines 7-12), such as ritonavir, or derivatives or analogs thereof (page 22, lines 14-22 and page 25, lines 3-6; see present claims 1-3), via the administration of such an inhibitor in a conventional dosage form (page 29, lines 3-8; see present claim 12), further comprising a pharmaceutically, cosmetically or dermatologically acceptable carrier or diluent (page 29, lines 3-8; see present claim 12), to a human or other animal in an amount sufficient to produce a therapeutic effect (page 29, lines 1-3; see present claim 1) and, further, may be administered in combination with other anti-cancer chemotherapeutic treatments (page 33, lines 21-23; see present claims 14-17).

The Merck Index is relied upon to show that the protease inhibitor ritonavir taught by Weichold et al. is synonymous with the chemical structure of formula I (see pages 1418-1419) as set forth in present claim 1.

In light of the fact that Weichold et al. expressly teach that "at least one PR-I [HIV-1 protease inhibitor]' may be administered for the effective treatment of cancer, such is considered

to clearly teach the use of one PR-I inhibitor (i.e., ritonavir) alone and, thus, in the absence (i.e., not in combination with) of any one or more other PR-I inhibitor(s), such as those compounds of formula II-V as recited in present claims 2-3.

Furthermore, Weichold et al. expressly teach the use of the disclosed HIV-1 protease inhibitors in normal, non-immune compromised mice (see Figures 27a and 27b at page 21 of the specification and page 26 of the attached drawings). Weichold et al. also teach, "...the inventors have observed the surprising and unexpected phenomenon that HIV-1 protease inhibitors (PR-I) and proteasome inhibitors are potent immune modulators. The ability of PR-I to modulate the immune system is independent of HIV-1 protease inhibition and is not related to HIV infection, since similar effects were observed in HIV free experimental systems." (see Weichold et al., page 26, lines 22-27) Thus, it is clear that the concept of treating a non-HIV positive subject (since the same immune modulating effects were shown in hosts with or without HIV) via the methods of the disclosed invention was within the scope of the Weichold et al. reference and would have placed such a concept well within the possession of the public.

Moreover, it is noted that Applicant has failed to define the cancers that are "associated with resistance to known anticancer drug regimens" as recited in present claims 28-29. In light of such a fact, the claims have been interpreted to read upon the specific types of cancer that are recited in present claim 27 (see "II" above under the heading "Claim Rejections-35 U.S.C. 112, Second Paragraph), which, for the reasons stated above, are properly anticipated by Weichold et al.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 12-14, 16-17, 27-29 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weichold et al. (WO 00/33654; 2000) in light of The Merck Index (cited to show a fact) in view of Remington's Pharmaceutical Sciences (1980), Ojima et al. (U.S. Patent No. 5,811,452; 1998) and Hurst et al. ("Lopinavir", *Drugs*, 2000).

Weichold et al. teach a method of treating pancreatic (page 33, line 25), lung (page 33, line 25), breast (page 33, line 25), head and neck (page 33, line 26), prostate (page 33, line 25), colon (page 33, line 26), stomach (page 33, line 25), ovarian (page 33, line 26) and brain cancer (page 33, line 26; see present claims 1 and 27 for each of the previously named cancer types) using at least one HIV-1 protease inhibitor (page 33, lines 7-12), such as ritonavir, or derivatives or analogs thereof (page 22, lines 14-22 and page 25, lines 3-6; corresponds to Applicant's presently claimed compound of formula I and considered to meet Applicant's limitation of "prodrug" as recited in present claims 1-3), via the administration of such an inhibitor in a conventional dosage form (page 29, lines 3-8; see present claim 12), further comprising a pharmaceutically, cosmetically or dermatologically acceptable carrier or diluent (page 29, lines 3-8; see present claim 12), to a human or other animal in an amount sufficient to produce a therapeutic effect (page 29, lines 1-3; see present claim 1) and, further, may be administered in

combination with other anti-cancer chemotherapeutic treatments (page 33, lines 21-23; see present claims 14-17).

The differences between the Weichold et al. reference and the presently claimed subject matter lie in that the reference does not teach:

(i) salts of the compound of Formula I (see present claims 1-3) or the use of saline as a physiologically acceptable saline as a carrier, excipient or diluent (see present claim 13); or

(ii) the concomitant administration of a compound of Formula II in an amount four times the weight of the compound of Formula I (see present claims 4-5) or the concomitant administration of paclitaxel or docetaxel (see present claims 16-17).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) The use of pharmaceutically acceptable salts of ritonavir would have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been obvious to the skilled artisan motivated by any one or more of these factors to formulate the active agent ritonavir into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of

the agent in salt form would have been the same or substantially similar to that of the agent itself.

Furthermore, Ojima et al. (U.S. Patent No. 5,811,452; 1998) is cited to show that saline was a conventional pharmaceutically acceptable excipient used for the preparation of formulations suitable for parenteral or injectable administration (col.24, lines 12-18).

In light of such a teaching, and further in light of the fact that Weichold et al. teaches parenteral administration (see page 29, lines 12-18) and the use of any conventional pharmaceutically acceptable carrier in the formulation of a conventional dosage form, the use of saline as a pharmaceutically acceptable carrier would have been *prima facie* obvious to the skilled artisan for the preparation of ritonavir compositions, particularly because saline was commonly used in the art as an excipient for parenteral dosage forms and would have provided, at minimum, adequate, if not optimum, dissolution of the active agent for administration.

(ii) Weichold et al. specifically teaches the administration of at least one HIV-1 protease inhibitor, and further states, "It is anticipated that the administration of one or more PR-Is will enhance cellular immune processes and immune surveillance, thereby potentially providing for the eradication and/or reduced number of malignant cells." (page 33, lines 7-12) Such is an express statement that more than one HIV-I protease inhibitor may be concomitantly administered and would have been reasonably expected to exert an enhanced effect when more than one PR-I agent was administered.

However, Weichold et al. is silent as to the particular combination of a compound of formula I (previously identified as "ritonavir", see above under "Claim Rejection-35 U.S.C. 102") and a compound of formula II, which has herein been identified as being synonymous with lopinavir (see Hurst et al. at page 1372).

Hurst et al. has been relied upon not only to show that presently claimed compound II is synonymous with the HIV-1 protease inhibitor lopinavir (see abstract of Hurst et al. at page 1371 and chemical structure at page 1372), but also to show that a coformulation of 400 mg of lopinavir and 100 mg of ritonavir (i.e., four times the amount of lopinavir than ritonavir; see present claim 5) was a commonly used HIV-1 protease inhibiting composition in the art, because the use of ritonavir inhibits the metabolism of lopinavir and, thus, significantly increases plasma concentrations of the drug (see Hurst et al., column 1, paragraph 3).

In light of such knowledge, the use of a combination of both lopinavir (i.e., a compound of Formula II) and ritonavir (i.e., a compound of Formula I) would have been *prima facie* obvious to the skilled artisan. Motivation to administer such compounds together flows logically from the efficacy demonstrated in the prior art that each of the compounds were known to have the same HIV-1 protease inhibiting function and, thus, would have potentiated the protease inhibiting effect when administered together. The skilled artisan would have had the reasonable expectation that the combination of both lopinavir and ritonavir would have achieved, at minimum, additive, if not synergistic, effects when combined. This is further supported by Weichold et al., who teaches that the protease inhibiting function would be enhanced with the administration of more than one protease inhibitor (see page 33, lines 7-12). In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

In addition, Weichold et al. expressly teaches that the protease inhibitors may be administered in conjunction with other anti-cancer treatments or chemotherapeutics. Although

Weichold et al. is silent as to the express use of paclitaxel or docetaxel, such agents were well known in the art as possessing significant anticancer efficacy.

In this regard, Ojima et al. (U.S. Patent No. 5,811,452; 1998) is cited to show that both TAXOL (paclitaxel) and TAXOTERE (docetaxel) were known to have high cytotoxicity and strong antitumor activity against different cancers that are not effectively treated using conventional anticancer drugs (col.1, lines 62-65).

Thus, the use of paclitaxel or docetaxel in combination with ritonavir (i.e., a compound of Formula I) would have been *prima facie* obvious to the skilled artisan. Motivation to administer such compounds together flows logically from the efficacy demonstrated in the prior art that each of the compounds were known to have the same anticancer activity and, thus, would have potentiated the anti-tumorigenic function when administered in conjunction with one another. The skilled artisan would have had the reasonable expectation that the combination of paclitaxel or docetaxel and ritonavir would have achieved, at minimum, additive, if not synergistic, effects when combined. In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Conclusion

Rejection of claims 1-5, 12-14, 16-17, 27-29 and 60 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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